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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,802	11/09/2001	Anne Chew	MWH-0002US2	7301

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,802	CHEW ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-29* is/are pending in the application.

4a) Of the above claim(s) *25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group II in the paper filed 4/23/03 is acknowledged. The traversal is on the ground(s) that the inventions are not distinct because they are not properly separately classified and they do not require separate fields of search. This is not found persuasive because the inventions are properly separately classified and they do require separate fields of search. The invention of group II, now claims 26-29 is drawn to a method which requires the genotyping of an individual and then requires a number of complicated computational and comparative steps. The steps required in the methods of predicting haplotype pairs are clearly most suited for analysis using a computer and therefore are properly classified in 702/19, even though the initial step of genotyping maybe a molecular analysis, the overall claimed methodology is one of a bioinformatic process. For example, step "b" enumerating all possible haplotype pairs based on the genotyping of thirty nine different polymorphic sites. When considering 39 polymorphic sites, there are 5.5 billion different haplotypes that might arise in a population, and beyond that there are trillions of pairings possible of these haplotypes. Thus, the enumerating step, is a significant claim recitation of a data processing step, and the methods of claim 26-29 are properly classified in 702/19

Turning to the invention of group IV, applicants note that they do not understand the classification of claim 25 to 435/6 based on the manual of classification definition of the subclass. The claim is properly classified in this class insofar as "microorganism" in the definition of the class includes animal cells, and the nucleic acids being tested herein are at least derived from animal cells, and broadly interpreted the haplotyping processes of group IV involve

the testing of the nucleic acids of animal cells (which are included as microorganisms in the classification definitions). Nucleic acid analysis methods, including hybridization methods are included in class 435, subclass 6. Although the methods of group II could be cross referenced into this subclass, they are properly placed in 702/19 for the reasons previously discussed. Thus, contrary to the arguments provided, the separate classification of groups II and IV is appropriate.

Applicant asserts that the method of independent claim 25 will be achieved by the methods of predicting a haplotype pair of claim 26. However, the examiner does not agree. The methods of group II do not require actually haplotyping an individual, they predict a haplotype, in other words they make an educated guess at the haplotype. The methods of claim 25, on the other hand require an actual determination of the haplotype of an individual.

Applicants assert that because the classification of the two inventions is improper no prima facie search burden has been established. However, as discussed, the classification is proper, and thus, the examiner maintains the position that a prima facie search burden has been established. Even if both inventions were classified in 435/6, they would still require separate search in view of their separate goals and method steps as is evident from a review of the claims. It is further noted, as it was in the restriction requirement, that group IV contains within it 53 separate and distinct inventions, while group II is drawn to a single distinct invention. Though some of the references used to consider the two inventions may be in common, different considerations under each of the statues would be required in order to examine the distinct inventions.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 26-29 are examined herein. Claim 25 is withdrawn from prosecution.

Claim Rejections - 35 USC § 101 and 112

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 26-29 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The claims are drawn to methods for predicting a haplotype pair of an individual for the Interleukin 4 Receptor Alpha gene (IL4Rα). The specification does not appear to contain a clear assertion of a utility for the claimed methods, other than the fact that the claimed methods can in fact be used to predict which haplotype pair is present in an individual's genome.

The specification teaches a set of polymorphic sites within the IL4Rα gene that were identified by sequencing portions of the IL4Rα from two reference populations (referred to in the examples as Index Repository IA (example 1a) and another population of 70 human individuals (example 1b). The positions of the polymorphic sites within a reference sequence are given in Table 3, and illustrated in Figure 1. In example 2, Table 4, the specification provides a sampling of different genotypes containing the polymorphisms that were observed in the reference population, specifically teaching haplotype pairs that were determined using a "derivation protocol." Table 4 contains a listing of haplotype pairs observed in the reference populations for 39 polymorphic sites, but Table 4 also contains some blanks where particular alleles are not identified. The specification teaches that these can typically "be inferred based on linkage

disequilibrium and/or Mendelian inheritance." Example 2 teaches that the haplotype pairs were estimated from the unphased genotypes using an extension of Clark's algorithm. Thus, the haplotype pairs presented in Table 4 are not themselves empirically observed haplotype pairs but are an estimation that were deconvulated based on unphased genotypes.

Turning to the method of the claimed invention, the specification asserts that the "polymorphism and haplotype data disclosed herein are useful for studying population diversity, anthropological lineage, the significance of diversity and lineage at the phenotypic level, paternity testing, forensic applications, and for identifying associations between the IL4Rα genetic variation and a trait such as level of drug response or susceptibility of disease." These utilities are not particularly asserted as utilities for the claimed invention (as they are asserted utilities for data, not a method), nonetheless it is noted that these utilities are neither specific nor substantial with regard to the claimed invention. They are not specific to the claimed invention because they could be applied to any set of genetic markers in any gene for the partitioning of human populations. They are not substantial because they are an invitation to do further research in order to determine if the haplotype pairs disclosed herein are actually useful for any particular method.

Once one has carried out the method of the claimed invention and "assigned a haplotype pair to an individual that is consistent with the data," one has essentially assigned an arbitrary identifier to the gene of an individual. There is no particular relevance disclosed in the specification for any particular predicted haplotype pair. The prediction method herein is a method which results in the assignment of a haplotype pair to an individual simply for no end other than to make the assignment. Furthermore, it is noted that the methods are drawn to

"predicting" a haplotype pair, and do not necessarily assign an accurate haplotype pair to an individual, but instead result in the assignment of a haplotype pair that is "consistent with the data" in table 4. The data in table 4 themselves are not empirical data but are an estimation of possible haplotype pairs in a population, and thus the assignment of a predicted haplotype pair based on that data is another step away from an actual empirical determination of the haplotype pair present in an individual's genome. Furthermore, the data in table 4 are not complete, leaving the identity of a polymorphism present in some polymorphic sites blank to be inferred by "mendelian genetics or linkage disequlibrium." Thus, on another level, since the method is actually one more of "estimation" of a haplotype pair present in an individual than a method of actually determining that any particular haplotype pair is present in the genome of an individual, it is further clear that there is no specific or substantial utility for the arbitrary assignment of a haplotype pair label for an individual.

Claims 26-29 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The breadth of the claims and the teachings provided in the specification with regard to the asserted utilities of the instant invention are previously discussed in the rejection under 35 U.S.C. 101. The specification does not provide a single working example wherein the instant method is used in any real world context, but instead only postulates that the haplotype data in the specification may be useful in a variety of methods directed at determining if in fact the disclosed haplotypes are associated with any biological phenotype or phenomena of interest.

Essentially, the haplotype prediction of the claimed method is a method wherein a putative haplotpye pair is predicted for an individual based on two layers of estimations and assumptions. The first layer is the layer wherein the haplotype pairs of table 4 themselves were derived using a convolution analysis, that is, the haplotype pairs were not empirically observed, but were statistically predicted. The second layer is the prediction itself, which is also based on an analysis of predicted haplotype pairs in a sample. In order to reasonably confirm the validity of the haplotype prediction method, a large quantity of experimentation would be required by the skilled artisan, for example, the direct sequencing of hundreds of copies of the IL4Rα from different individuals to actually empirically determine the haplotype pairs present in a population. Furthermore, even after the validity of the methods of predicting the haplotype pair were confirmed, one skilled in the art still would have only a method for assigning an arbitrary identifier to an individual's IL4Rα gene copies. One still would not know the relevance of the fact that a particular individual has a "1, 2" haplotype pair. To determine how to use this invention would require experimentation which would result in determining some relevance of the actual haplotype assignment. Such experimentation in itself would be inventive, and thus the claims are also rejected under 112 1st paragraph for lack of provision of an enabling use for the claimed invention.

Even if applicant were to overcome the previous rejections and establish a patentable utility for the claimed invention, claims 26-29 would be further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for predicting a haplotype pair for the IL4Rα gene wherein the identifying step of part (a) utilizes methodologies wherein each of the polymorphic sites are directly genotyped, does not reasonably provide

enablement for method wherein the identifying step comprises indirectly determining the genotype of the polymorphic sites. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Breadth of the Claims

The rejected claims are drawn to a method of predicting a haplotype pair for the interleukin 4 receptor alpha (IL4Rα) of an individual and comprise a first step of "identifying the IL4Rα genotype for the individual" at each of thirty-nine different polymorphic sites. The specification teaches that such genotyping can occur via direct methods of direct detection of polymorphic sites, including for example, primer extension assays, an allele-specific PCR, a nucleic acid amplification assay, a sequencing assay, etc.. The specification also asserts that a the identity of an allele present at a polymorphic site can be "indirectly determined by genotyping a polymorphic site not disclosed herein that it is linkage disequilibrium with the polymorphic site that is of interest (p. 49)," and specifically recited in claim 29. Each of the claims rejected herein encompass methods wherein the identification of polymorphic sites occurs by such indirect determination.

Guidance in the specification and Working Examples

The specification teaches a set of polymorphic sites within the IL4Rα gene that were identified by sequencing portions of the IL4Rα from two reference populations (referred to in the examples as Index Repository IA (example 1a) and another population of 70 human individuals (example 1b). The positions of the polymorphic sites within a reference sequence are given in Table 3, and illustrated in Figure 1. In example 2, Table 4, the specification provides a sampling

of different genotypes containing the polymorphisms that were observed in the reference population, specifically teaching haplotype pairs that were determined using a "derivation protocol." Table 4 contains a listing of haplotype pairs observed in the reference populations for 39 polymorphic sites, but Table 4 also contains some blanks where particular alleles are not identified. The specification teaches that these can typically "be inferred based on linkage disequilibrium and/or Mendelian inheritance." Example 2 teaches that the haplotype pairs were estimated from the unphased genotypes using an extension of Clark's algorithm. Thus, the haplotype pairs presented in Table 4 are not themselves empirically observed haplotype pairs but are an estimation that were deconvulated based on unphased genotypes.

The specification does not, however provide any further guidance as to how to accomplish the identification of a genotype by indirect methodology based on linkage disequilibrium and/or Mendelian inheritance. In particular, the specification does not identify which of the disclosed polymorphisms are in linkage disequilibrium with one another such that the identity of one can reliably be used to predict the identity of another, and further, the specification does not provide any guidance as to any polymorphisms outside of those identified as particular polymorphic sites in the specification that might be in linkage disequilibrium with the recited polymorphic sites. While the description clearly discloses that the identity of a nucleotide may be "determined" by examining a subset of polymorphic sites and inferring the identity of other polymorphic sites, the description never discloses which polymorphic site or sites must be examined in order for a skilled artisan to draw conclusions concerning the identity of other polymorphic sites.

The specification does not provide a working example wherein a genotype is identified using inferred identification of a polymorphic site either based on the identity of a polymorphic site disclosed herein or a polymorphic site not disclosed herein.

Guidance in the Prior Art

Lacking guidance from the specification, one of skill in the art may look to the teachings of the prior art for enablement of a claimed invention. The prior art as exemplified by Deichmann *et al.* (Biochemical and Biophysical Research Communications, 231, 696-697, 1997) discloses the detection and sequencing of the IL4Rα gene, and further disclose common polymorphisms within the coding region of the gene. However, the prior art does not disclose what particular polymorphism or combinations of polymorphism must be detected in order for one to reach a conclusion infer the identity of a remaining set of polymorphisms within an individual's genome. Accordingly, neither the description nor the art provide guidance with respect to which subsets of polymorphic sites must be examined to practice methods in which a genotypes at particular polymorphic sites is "identified" by examining a subset of polymorphic sites and making inferences to determine the remaining polymorphisms. Further, no guidance is provided as to which polymorphic sites outside of those identified herein as PS1-PS45 might possible be in linkage disequlibirum with any of the instantly disclosed polymorphic sites. Lacking this critical information, no quantity of experimentation would be sufficient to practice such methods of identifying an IL4Rα genotype for an individual at the 39 recited polymorphic sites using indirect means.

Level of Unpredictability and Quantity of Experimentation

Absent the undertaking of extensive experimentation and screening to determine which polymorphic sites are sufficiently predictive of one another within the set of 45 taught in the specification, and extensive screening of the regions of the genome surrounding the IL4Rα gene to determine additional polymorphic sites that are in linkage disequlibirium with the recited polymorphic sites, the practice of the claimed invention with regard to indirect determination and therefore the specification does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed step of "identifying an IL4Rα genotype" to be carried out by a person skilled in the art in a manner commensurate with the claims. Though the level of skill in the art is quite high, there is a higher level of unpredictability with regard to which polymorphic sites can be used as predictors of the identity of neighboring sites, and outside of the 45 polymorphic sites taught in the specification it is entirely unpredictable as to which of the polymorphic sites that are "not disclosed herein" but may be useful in the instant methods for predicting haplotype pairs.

Conclusion

Thus, in light of the breadth of the claims, the lack of working examples in the specification, the lack of guidance in the prior art, the high level of unpredictability in the art and the high quantity of experimentation required, , it is concluded that undue experimentation would be to practice the claimed invention commensurate in scope with the instant claims, even if all concerns regarding the utility of the claimed invention were overcome.

Conclusion

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Switzer
Examiner
Art Unit 1634

July 9, 2003